HIGHLIGHTS OF MYELOMA ROUNDS

TARGET AUDIENCE
This CE activity is intended for hematologists-oncologists, medical oncologists, nurse practitioners, nurses and pharmacists involved in the care of patients with myeloma.

EDUCATIONAL OBJECTIVES
After completing this CE activity, the participant should be better able to:

- Describe the latest developments in myeloma, including current and emerging treatments
- Engage patients and caregivers in discussions on clinical trials, newly approved therapies and emerging therapies for myeloma, including combination therapies, CAR T-cell therapy and bispecific antibodies
- Identify strategies for optimal patient care
- Apply evidence-based treatment strategies
- Access patient support resources
SPEAKERS

Edward A. Stadtmauer, MD (Chair, Myeloma Rounds, Philadelphia)
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow, and Shaffer Families’
President's Distinguished Professor
University of Pennsylvania Abramson Cancer Center
Philadelphia, PA

Cindy Varga, MD (Chair, Myeloma Rounds, Winston-Salem)
Associate Professor
Atrium Health Levine Cancer Institute
Plasma Cell Dyscrasia Division
Department of Hematology and Oncology
Charlotte, NC

Highlights of Myeloma Rounds
Updates in Clinical Research in 2023

Cindy Varga, MD
Associate Professor
Atrium Health Levine Cancer Institute
Plasma Cell Dyscrasia Division
Department of Hematology and Oncology
Charlotte, NC
INTRODUCTION

- Maintenance lenalidomide post ASCT is currently the standard of care
- About 25% of patients will discontinue Len maintenance due to poor tolerance or adverse events
- There is unmet need for improved maintenance drugs with better efficacy and tolerability
- Iberdomide is a novel oral cereblon E3 ligase modulator (CELMoD) with greater immunomodulatory effects than IMiDs
**EMN26**

- Eligibility criteria
  - IMid-PI induction
  - At least a PR after ASCT
- Primary endpoint:
  - Efficacy (response improvement within 6 mos)
- Secondary endpoints
  - MRD by NGF
  - Adverse events
  - PFS
**EMN26: Hematologic safety profile: cycles 1-12**

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>1.3 mg cohort (n=40)</th>
<th>1.0 mg cohort (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (10)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>3 (8)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

* The most common hematologic AE was neutropenia
  - There was only 1 case of febrile neutropenia in the 1.0 mg ibencoramide cohort

**EMN26: Non-hematologic safety profile: cycles 1-12**

**Most frequent (≥ 20% all grade) TEAEs and events of interest, n (%)**

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>1.3 mg cohort (n=40)</th>
<th>1.0 mg cohort (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (18)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>6 (15)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hyper/hypothyroidism</td>
<td>4 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Rash*</td>
<td>8 (20)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td>12 (33)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>COVID-19</td>
<td>7 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (8)</td>
<td>2 (5)*</td>
</tr>
</tbody>
</table>

*1 of 2 cases is PJP infection
** 1 of 2 cases is PJP infection

The majority of non-hematologic AEs were low grade
No second primary malignancies reported
Rash was transient and occurred mainly during first cycle
EMN26: Response improvement during first 6 cycles

1.3 mg cohort: Response improvement: 42%
1.0 mg cohort: Response improvement: 35%

MRD conversion*: 2/13 patients (15%) in 1.3 mg cohort and 4/17 patients (24%) in 1.0 mg cohort

Van De Donk et al. ASH Annual Meeting, Abstract #208

EMN26: Response improvement during first 12 cycles

1.3 mg cohort: Response improvement: 50%
1.0 mg cohort: Response improvement: 54%

MRD conversion*: 7/12 patients (58%) in 1.3 mg cohort and 5/17 patients (29%) in 1.0 mg cohort

Van De Donk et al. ASH Annual Meeting, Abstract #208
CONCLUSIONS

- Iberdomide maintenance results in an improvement in response over time in patients who received IMiD/PI-based induction +/- antiCD38 and ASCT
  - Iberdomide demonstrate at least a 50% improvement of response at cycle 12
  - Len demonstrated 31% improvement of response at cycle 12 in the EMN02 trial
- Promising MRD conversion data with iberdomide post ASCT was observed
- Iberdomide showed manageable toxicity
- Excalibur trial
  - Ongoing phase III registrational trial of iberdomide vs. lenalidomide maintenance post transplant (NCT05827016)
NON-INVASIVE MRD TESTING

Investigate the complementarity and prognostic value of new multimodal minimally invasive MRD assessment in MM

N = 242
Maintenance or observation PETHEMA/GEM Clinical trials

PB
n = 242/242
CTCs

Plasma cfDNA
n = 27/242
Mutations

Serum
n = 168/242
M-component

Gonzalez et al. ASH Annual Meeting 2023 Abstract #0339
Prognostic value of MRD assessment using BloodFlow
MRD+ associated with 12-fold increment in the risk of progression and/or death

<table>
<thead>
<tr>
<th>MRD</th>
<th>No.</th>
<th>Median PFS</th>
<th>PFS @1y</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>220</td>
<td>NR</td>
<td>94%</td>
<td>11.7 (P &lt; .001)</td>
</tr>
<tr>
<td>Positive</td>
<td>22</td>
<td>3 mo</td>
<td>46%</td>
<td></td>
</tr>
</tbody>
</table>

Time since MRD assessment (months)

MRD assessment in PB using BloodFlow and in BM using NGF
Analysis restricted to 136 patients with paired samples

<table>
<thead>
<tr>
<th>MRD PB / BM</th>
<th>No.</th>
<th>Median PFS</th>
<th>PFS @1y</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>- / -</td>
<td>99</td>
<td>NR</td>
<td>97%</td>
<td>-</td>
</tr>
<tr>
<td>- / + &amp; +/-</td>
<td>26</td>
<td>NR</td>
<td>88%</td>
<td>3.4 (P = .14)</td>
</tr>
<tr>
<td>+ / +</td>
<td>11</td>
<td>3 mo</td>
<td>45%</td>
<td>19.7 (P &lt; .001)</td>
</tr>
</tbody>
</table>

Time since MRD assessment (months)
BloodFlow and QIP-MS showed more balanced NPV and PPV
CloneSight showed the highest PPV but low NPV

<table>
<thead>
<tr>
<th>BloodFlow</th>
<th>QIP-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>78% NPV</td>
<td>82% NPV</td>
</tr>
<tr>
<td>96% PPV</td>
<td>70.5% PPV</td>
</tr>
</tbody>
</table>

Are these methods complementary for improved prediction of PFS?

Complementarity between BloodFlow and QIP-MS
3/129 (2%) double negative MRD patients progressed thus far

<table>
<thead>
<tr>
<th>MRD BF &amp; QIP-MS</th>
<th>No.</th>
<th>Median PFS</th>
<th>PFS @1y</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/-</td>
<td>129</td>
<td>NR</td>
<td>98%</td>
<td>-</td>
</tr>
<tr>
<td>-/+</td>
<td>26</td>
<td>NR</td>
<td>60%</td>
<td>9.8 (P = .002)</td>
</tr>
<tr>
<td>+/−</td>
<td>2</td>
<td>2 mo</td>
<td>0%</td>
<td>97.7 (P &lt; .001)</td>
</tr>
<tr>
<td>+/+</td>
<td>11</td>
<td>8 mo</td>
<td>46%</td>
<td>29.5 (P &lt; .001)</td>
</tr>
</tbody>
</table>

Double-negative MRD detection in PB and serum using BloodFlow and QIP-MS achieved a NPV of 84% (ie, MRD negativity in BM using NGF)
CONCLUSIONS

- BloodFlow and QIP-MS are empowered to detect MRD with high sensitivity in PB and serum
- The presence of CTCs was systematically associated with dismal PFS
- BloodFlow showed very high PPV and QIP-MS achieved the highest NPV
- The complementarity between these methods enabled the identification of multimodal MRD negative patients with very low risk of relapse
- This study paves the way towards minimally invasive MRD assessment in MM patients on maintenance or observation

ATLAS trial

Key eligibility criteria:
- ≤100 days after HSCT
- ≤17 months after diagnosis
- ≤2 induction regimens
- ≥10% after HSCT

Methods

Kučiči et al. ASH Annual Meeting 2023 Abstract #0340
MS (-) status post cycle 18 was associated with superior progression-free survival (PFS)

Number at risk:
- MS(-): 68, 58, 29, 9, 0
- MS(+): 28, 20, 8, 2, 0

Double (MS and MRD) negativity is associated with favorable outcomes

NGS
Threshold: $10^{-5}$

MFC
Threshold: $10^{-5}$

MFC and MS

NGS and MS
CONCLUSIONS

- **MS-based disease assessment** in the post ASCT setting maybe feasible.
- Prognostic significance of MS negativity increase with time.
- MS is **complementing BM-based MRD assessments**.
- Further **prospective studies** are needed confirm these conclusions.
Highlights of Myeloma Rounds
Initial Therapy of Multiple Myeloma

Edward A. Stadtmauer, MD
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow, and Shaffer Families’
President’s Distinguished Professor
University of Pennsylvania Abramson Cancer Center
Philadelphia, PA

CASE PRESENTATION

- 9/12/22: 35 yo AA woman with hx of pituitary adenoma and HTN presented to PCP with right shoulder pain. X-ray was unremarkable. Referred to Ortho.
- 11/28/22: Repeat x-ray showed large lytic lesion of right proximal humerus. MRI showed 7.5 x 4.6 x 4.7 cm lesion with complete replacement of acromion (Figure 1) and similar 4.3 x 2.4 x 4.8 cm mass replacing humeral head, both with extensive marrow replacement.
- 12/6/22: US-guided biopsy of right acromion mass shows sheets of small to intermediate sized atypical plasmacytoid cells that are CD38+, CD138+, CD117+ (subset) and CD79a+ (dim, small subset). Kappa and lambda ISH staining is weak. Ki-67 15%. Positive clonal IGH gene rearrangement.
- 12/7/22: CT CAP with large lucent lesion in T12 with possible inferior endplate fracture. Other small lucent lesions throughout skeleton.
- Hg 9.7, ca 12.7 alb 2.9, SPEP M-spike 3.9 g/dl IgG kappa, kappa 248.6, lambda 3.1, ratio 80.19, IgG 4221, B2M 4.91, LDH 247.
- 1/1-1/13/23: Admitted for intractable pain in right shoulder and lower back.
- 1/4/23: BM biopsy with hypercellular marrow (95%) and 80% involvement by kappa light chain-restricted plasma cells.
**DISEASE TRAJECTORY**

Nonmalignant Accumulation
- Stroma angiogenesis
  - Plasma Cell Leukemia
  - Extramedullary Disease

Malignant Transformation
- High-Risk 20, 20, 2
  - 20% PC
  - 2:1 ratio
  - 2+ g/dl M-spike

Aggressive and Stromal Independent
- Plasma Cell Leukemia
- Extramedullary Disease

**MGUS**
- <10% bone marrow plasma cells
- <30 g/L M-protein
- No SLiM CRAB
- 1%/yr risk of progression to MM

**Smoldering Myeloma**
- 10-60% bone marrow plasma cells
- No SLiM CRAB
- ≥30 g/L M-protein (IgG or IgA) OR
- ≥500 mg/24 hr urinary protein
- No amyloidosis
- High-Risk 20, 20, 2
  - 20% PC
  - 2:1 ratio
  - 2+ g/dl M-spike

**Multiple Myeloma**
- Clonal bone marrow ≥10% or bony/extramedullary plasmacytoma
- Any ≥ 1 SLiM CRAB feature (s):
  - SLiM*
    - S: Clonal plasma cells in BM ≥60%
  - Li: Serum free light-chain ratio ≥100 mg/L
  - M: >1 MRI focal lesion ≥5 mm
  - CRAB* feature:
    - C: Calcium elevation (>11 mg/dL)
    - R: Renal insufficiency (Cr>2 mg/dL or CrCl<40 mL/min)
    - A: Anemia (Hgb<10 g/L)
    - B: Bone disease: (≥1 lytic lesion)

**CYTOGENETIC CLASSIFICATION**

**STANDARD RISK**
- No abnormalities detected
- OR
  - Abnormalities detected are not defined as high risk

**HIGH RISK**
- Identified by FISH
  - t(4;14)
  - t(14;16)
  - t(14;20)
- 17/ (del 17p)
- gain(14)

- Identified by karyotyping
  - nonhyperdiploid karyotype
  - del(13)
- Genetic analysis
  - Double hit (biallelic TP53 inactivation or amplification of CKS1B [1q21])
- Other disease characteristics
  - Extramedullary disease
  - Plasma cell leukemia


NEW STAGING SYSTEM (R2-ISS)

- Addresses prognostic significance of +1q cytogenetic abnormality
- Contemporary cohorts (diagnosed 2005-2016)

### 1. B2M, Albumin

<table>
<thead>
<tr>
<th>ISS stage 1</th>
<th>B2M</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS stage 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS stage 3</td>
<td>&gt;5.5</td>
<td></td>
</tr>
</tbody>
</table>

### 2. Points

<table>
<thead>
<tr>
<th>ISS stage 1</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS stage 2</td>
<td></td>
</tr>
<tr>
<td>Del 17p</td>
<td>1</td>
</tr>
<tr>
<td>t(4:14)</td>
<td>1</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>1</td>
</tr>
<tr>
<td>Gain chr 1q</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### 3. Points, Stage, % pts, mPFS, mOS

<table>
<thead>
<tr>
<th>Points</th>
<th>Stage</th>
<th>% pts</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>19</td>
<td>68</td>
<td>NR</td>
</tr>
<tr>
<td>0.5-1</td>
<td>2</td>
<td>31</td>
<td>45</td>
<td>109</td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>3</td>
<td>41</td>
<td>30</td>
<td>69</td>
</tr>
<tr>
<td>3-5</td>
<td>4</td>
<td>9</td>
<td>20</td>
<td>38</td>
</tr>
</tbody>
</table>


B2M, beta-2 macroglobulin; mOS, median overall survival; mPFS, median progression-free survival

- Addresses prognostic significance of +1q cytogenetic abnormality
- Contemporary cohorts (diagnosed 2005-2016)
Multiple myeloma is highly complex during progression and relapse due to genomic events and clonal evolution.

**THE TRAJECTORY OF MYELOMA**

Asymptomatic

<table>
<thead>
<tr>
<th>M protein (g/L)</th>
<th>0</th>
<th>20</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
</table>

MGUS or smoldering myeloma

**ACTIVE MYELOMA**

1. RELAPSE

Plateau remission

2. RELAPSE

REFRACTORY RELAPSE

First-line therapy

Second line

Third line

**ACTIVE MYELOMA**

**SWOG S0777**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>First line</th>
<th>Second line</th>
<th>Third line</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVd (8 x 21 days)(N=230)</td>
<td>Rd (6 x 28 days)(N=242)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg days 1-14</td>
<td>25 mg days 1-21 of 28</td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² days 1, 4, 8, 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20 mg days 1, 2, 4, 5, 11, 12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>25 mg days 1-21 of 28 + dex. 40 mg days 1, 8, 15</td>
</tr>
</tbody>
</table>

44% age >65; 69% intent to transplant; 33% ISS stage 3; CrCl ≥30 mL/min

**Median PFS**

43 vs. 30 months

HR 0.712

**Overall survival**

Durie et al., Lancet, 2016

Durie et al., Blood Cancer Journal (2020) 10(53)
S0777 TOLERABILITY IN OLDER PATIENTS;
BORTEZOMIB SCHEDULE

- Once weekly bortezomib: Same OS/PFS, less peripheral neuropathy.
- Twice weekly bortezomib: Faster time to best response
- We often start with twice weekly dosing and switch to once weekly dosing after 1-2 cycles in patients with symptomatic complications.

### Subgroup analysis of SWOG S0777 by age

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age &lt;65 years (n=250)</th>
<th>Age ≥65 years (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival (PFS)</td>
<td>VRd (n=120)</td>
<td>VRd (n=109)</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>55.4 months</td>
<td>39.6 months</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.63 (0.49, 0.83)</td>
<td>Reference</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>0.61 (0.43, 0.84)</td>
<td>Reference</td>
</tr>
<tr>
<td>Overall survival (OS)</td>
<td>VRd (n=120)</td>
<td>VRd (n=109)</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>64.9 months</td>
<td>62.9 months</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.61 (0.49, 0.83)</td>
<td>Reference</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>0.60 (0.47, 0.86)</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Subgroup analysis of SWOG S0777 by age

- Incidence of grade ≥3 treatment-emergent adverse events
- Incidence of treatment discontinuation due to toxicity

### CARFILZOMIB IN FIRST-LINE THERAPY

**ENDURANCE (ECOG E1A11)**

- Newly diagnosed MM, standard-risk N=1053
- Induction: 36 weeks
- Maintenance
  - VRd
  - KRd
  - Len x 24m
  - Len until PD

### Cardiopulmonary/Renal Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>P&lt;0.001</th>
<th>0.0015</th>
<th>0.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRd</td>
<td>16.1</td>
<td>53.4</td>
<td>24.4</td>
</tr>
<tr>
<td>KRd</td>
<td>4.8</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Len x 24m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Len until PD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>P&lt;0.001</th>
<th>0.0015</th>
<th>0.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRd</td>
<td>16.1</td>
<td>53.4</td>
<td>24.4</td>
</tr>
<tr>
<td>KRd</td>
<td>4.8</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Len x 24m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Len until PD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kumar et al., Lancet Oncology (2020) 21:1317

ASCO 2020 LBA3
HIGH-DOSE MELPHALAN + AUTO SCT CONSOLIDATION FORTE TRIAL

Among pts receiving subsequent therapy, 46% of control group received daratumumab at some point.

DARATUMUMAB IN NEWLY DIAGNOSED, TRANSPLANT-INELIGIBLE MM: MAIA
### DARATUMUMAB + VRD

**GRIFFIN STUDY**

**Primary endpoint:** sCR by end of consolidation

**Secondary endpoints:** MRD, ORR, PFS, OS

**Induction:** Cycles 1-4

- **D-VRd**

**Consolidation:** Cycles 5-6

- **D-VRd**

**Maintenance:** Cycles 7-32

- **D-R in 28-day cycles**

**Progression-free Survival**

**Overall Survival**

<table>
<thead>
<tr>
<th>ORR post ind.</th>
<th>D-VRd</th>
<th>VRd</th>
</tr>
</thead>
<tbody>
<tr>
<td>98%</td>
<td>98%</td>
<td>92%</td>
</tr>
<tr>
<td>sCR post cons.</td>
<td>42%</td>
<td>32%</td>
</tr>
<tr>
<td>sCR end of study (p=0.0005)</td>
<td>67%</td>
<td>48%</td>
</tr>
</tbody>
</table>

- **Median follow-up:** 49.6 months
- **3-year OS rate:** 92.7%
- **4-year OS rate:** 92.2%
- **HR: 0.90 (95% CI: 0.31-2.56)**
- **P = 0.8408**

**Infections over time by treatment cycle**

- More infections with D-RVd but no difference in high-grade infections
PERSEUS: Study VRd +/- Daratumumab, ASCT, R +/- D

- Multicenter, open-label, randomized phase III trial; current analysis median f/u: 47.5 mo

**Induction: Cycles 1-4 (28-day cycles)**

- D-VRd
  - D: 1800 mg SC QW/Q2W
  - V: 1.3 mg/m² SC D1, 4, 8, 11
  - R: 25 mg PO D1-21
  - d: 40 mg PO/IV D1-4, 9-12 (n = 355)

- VRd
  - V: 1.3 mg/m² SC D1, 4, 8, 11
  - R: 25 mg PO D1-21
  - d: 40 mg PO/IV D1-4, 9-12 (n = 354)

**Consolidation: Cycles 5-6 (28-day cycles)**

- D-VRd: as in induction
- VRd: as in induction

**Maintenance: Cycles 7+ (28-day cycles)**

- D-R: 1800 mg SC Q2W
  - R: 10 mg PO D1-28

- R: 10 mg PO D1-28 until PD
  - MRD+ Discontinue D
  - MRD- Continue D

**Primary endpoint:** PFS

**Key secondary endpoints:** ≥CR rate, MRD negativity rate, OS

* QW during cycles 1-2, Q2W during cycles 3-4. D discontinued after ≥24 mo in patients with ≥CR and 12 mo sustained MRD negativity; D restarted upon confirmed loss of CR without PD or MRD recurrence.


---

PERSEUS: Study VRd +/- Daratumumab, ASCT, R +/- D

Efficacy Outcome | D-VRd (n = 355) | VRd (n = 354) | OR (95% CI) | P Value
---|---|---|---|---
≥CR, % | 87.9 | 70.1 | 3.13 (2.11-4.65) | <.001
  sCR | 69.3 | 44.6 |
  CR | 18.6 | 25.4 |
MRD negativity, %
  10⁻¹ | 75.2 | 47.5 | 3.40 (2.47-4.69) | <.0001
  10⁻² | 65.1 | 32.2 | 3.97 (2.90-5.43) | <.0001
Sustained MRD negativity (10⁻²) ≥12 mo, % | 64.8 | 29.7 | 4.42 (3.22-6.08) | <.0001

48-mo PFS rate: 84.3% vs 67.7% (HR: 0.42; P < .0001)

≥CR rate: 87.9% vs 70.1% (P < .001)
MRD negativity (10⁻⁵) rate: 75.2% vs 47.5% (P < .001)
64% on D-R maintenance for ≥ 2 yr stopped D after achieving sustained MRD negativity

Secondary malignancies occurred in 10.7% (37) of patients in the D-VRd arm and 7.2% (n = 25) in the VRd arm
Increased respiratory infections and pneumonias

Sonneveld. ASH 2023; Abstr LBA-1. Sonneveld. NEJM. 2023;[Epub].
ISKIA EMN24: STUDY DESIGN

Primary endpoint: MRD negativity by NGS after post-ASCT consolidation
Secondary endpoints: MRD negativity after induction, PFS, sustained MRD negativity

- Compared with KRd, IsaKRd resulted in significantly higher postconsolidation 10-5 and 10-6 MRD negativity rates
- Higher rates of 10-5 and 10-6 MRD negativity observed after each treatment phase (induction, transplantation, consolidation)
- 10-5 and 10-6 MRD negativity increases observed in all subgroups, including high-risk and very high-risk disease
- No new safety issues identified with IsaKRd

INITIAL THERAPY CONCLUSIONS

- Dara-VRD, VRd and dara-Rd are excellent options for first-line therapy supported by large, phase 3, RCTs
  - VRd → inadequate response → add daratumumab
  - Dara-Rd → inadequate response → add bortezomib
- Dara-Rd is preferred for older, transplant-ineligible population
- Emerging data for Dara-VRd for all patients especially with high-risk disease or aggressive initial presentation.
- Carfilzomib has limited role in first-line therapy [ECOG E1A11]
  - KRd has comparable PFS to VRd
  - Less peripheral neuropathy but higher cardiac and renal toxicity
  - CD38-KRD deeper response than KRD
**SUMMARY OF OUR APPROACH TO FIRST-LINE THERAPY**

**Initial therapy**

- **Young, transplant-eligible**: Dara-VRd or VRd
- **High-risk or morbid initial presentation**: Dara-VRd <PR after C2
- **Renal failure (CrCl <30)**: Dara-CyBorD
- **Transplant-ineligible, older**: Dara-Rd <PR → Dara-VRd

**Transplant eligible**: High-dose melphalan + auto SCT

**Transplant ineligible**: Consider maintenance lenalidomide (or bortezomib) for PFS benefit

**VZV and DVT prophylaxis, Zolendronic acid or denosumab bone health maintenance**

---

**CASE**

- **1/4/23**: Bortezomib 1.3 mg/m² (days 1, 4, and 8) and dexamethasone 40 mg daily x 4 days w/ acyclovir prophylaxis. Leuprolide for oncofertility (no time for egg preservation).
- **1/6/23**: Palliative RT to right shoulder and left humerus for pain control.
- **1/10/23**: IR-guided T12 percutaneous vertebroplasty.
- Discharged with pain regimen and plan for D-VRd as outpatient as per GRIFFIN trial.
- Lenalidomide to start post-IUD placement.
- Abnormal with gains of chromosomes or segments 1q (3 copies), 9, 17p and 19 and losses of 8p, 16p and 17p in mixed states representing clonal diversity.
- **NGS**: APC (7.0%), BRCA2 (51.3%; VUS), CARD11 (9.3%), DOT1L (13.2%), two ERBB2 variants (5.0% and 5.6%), ETV6 (49.7%), two GEN1 variants (49.7% and 51.7%), KMT2C (49.2%), MYCL (4.8%), NTRK3 (46.5%), PBRM1 (47.2%), PIK3R2 (8.2%), TET2 (6.6%), WHSC1 (5.9%).
- **FISH**: Positive for t(14;16) in 57 of 100 cells, 17p/TP53 deletion in 23 of 100 cells, IGH rearrangement in 59 cells of 100 cells.
- **R-ISS Stage II** (42 months median progression-free survival) with triple hit myeloma.
CASE

- 1/16/23: C2 D-Vd
- 1/24/23: Started lenalidomide with aspirin prophylaxis; held on 1/31/23 for orthopedic surgery on 2/8/23.
- Pulse dexamethasone 40 mg x 4 days.
- Worse low back pain worse → MRI with new lesions in T7, T8, T10, T11, L1, and sacrum. New T8 pathologic compression fracture with partial retropulsion at T8 and T12 causing mild to moderate canal stenosis. M-spike 3.2
- Initiated KD-PACE based on ultra-high-risk cytogenetic profile (C1 completed 3/30/23).
- 4/6/23: Repeat BM biopsy with hypercellular marrow (85%) with trilineage hematopoiesis due to growth factor support without evidence of plasma cell neoplasm. CMA without high-risk cytogenetics.
- 4/18/23: Stem cell collection (target 8 million CD34 cells/kg; collected 15.61 million CD34 cells/kg).
- 4/24/23: Melphalan-conditioned autoHSCT (possible tandem autoHSCT pending MRD status), followed by KR maintenance until progression.

Highlights of Myeloma Rounds
Sequencing of Bispecifics and CARTS

Cindy Varga, MD
Associate Professor
Atrium Health Levine Cancer Institute
Plasma Cell Dyscrasia Division
Department of Hematology and Oncology
Charlotte, NC
CASE

- 67F with IgG kappa MM, R-ISS III, diagnosed in 2019
  - Normal FISH
  - Extensive plasmacytomas of the bone and spine
- s/p XRT at multiple sites
- s/p multiple lines of therapy:
  - 6/2019 - 1/2020: RVD
  - 1/2021-12/2021: Dara-Kd
  - 2/2022-10/2022: Cy-Pom-Dex

WHAT SHOULD NEXT THERAPY BE?

- 12/22/22: TNB383 on clinical trial
- 01/04/23: Rapidly enlarging paramedullary lesions
  - L jaw mass, cranial nerve 7 palsy, sacral mass and large sternal mass
MECHANISMS OF RESISTANCE

- Decreased antigen expression
- T Cell exhaustion, possibly exacerbated by previous lines of therapy
- Tumor microenvironment

RECENT FDA APPROVALS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Target</th>
<th>Date</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ide-cel</td>
<td>CART</td>
<td>BCMA</td>
<td>March 26, 2021</td>
<td>Following 4 or more lines</td>
</tr>
<tr>
<td>Cilta-cel</td>
<td>CART</td>
<td>BCMA</td>
<td>February 28, 2002</td>
<td>Following 4 or more lines</td>
</tr>
<tr>
<td>Teclistamab</td>
<td>BiAb</td>
<td>BCMA</td>
<td>October 25, 2002</td>
<td>Following 4 or more lines</td>
</tr>
<tr>
<td>Talquetamab</td>
<td>BiAb</td>
<td>GPRC5D</td>
<td>August 9, 2023</td>
<td>Following 4 or more lines</td>
</tr>
<tr>
<td>Erlantamab</td>
<td>BiAb</td>
<td>BCMA</td>
<td>August 14, 2023</td>
<td>Following 4 or more lines</td>
</tr>
</tbody>
</table>
### BISPECIFIC AB V. CAR T

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bispecific Abs</td>
<td>Off the shelf</td>
<td>Continuous dosing</td>
</tr>
<tr>
<td></td>
<td>Lower rates of ICANS/CRS</td>
<td>Lower ORR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infections</td>
</tr>
<tr>
<td>CART</td>
<td>One time dose</td>
<td>Higher CRS/ICANS</td>
</tr>
<tr>
<td></td>
<td>Higher ORR</td>
<td>Manufacturing/Availability Issues</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infections</td>
</tr>
</tbody>
</table>

---

#### Table 3. Response to cilta-cel

<table>
<thead>
<tr>
<th></th>
<th>Full cohort (N = 20)</th>
<th>ADC exposed (N = 17)</th>
<th>Bispecific exposed (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>60.0 (91.8-90.9)</td>
<td>61.5 (91.8-90.9)</td>
<td>57.1 (91.8-90.9)</td>
</tr>
<tr>
<td>Best response, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenest complete response</td>
<td>1 (5.0)</td>
<td>1 (7.0)</td>
<td>0</td>
</tr>
<tr>
<td>Complete response</td>
<td>5 (25.0)</td>
<td>4 (23.5)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>3 (15.0)</td>
<td>3 (17.6)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (5.0)</td>
<td>0</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Minor response</td>
<td>1 (5.0)</td>
<td>0</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (15.0)</td>
<td>2 (11.8)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Progression disease</td>
<td>3 (15.0)</td>
<td>3 (17.6)</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable/lost</td>
<td>1 (5.0)</td>
<td>0</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>11.2(9.9-12.5)</td>
<td>8.6(9.3-12.5)</td>
<td>3.9(3.0-5.3)</td>
</tr>
<tr>
<td>Median duration (95% CI)</td>
<td>11.5 (9-16.9)</td>
<td>11.0 (9-16.9)</td>
<td>8.2 (4.4-16.9)</td>
</tr>
<tr>
<td>Median time to first response (95% CI)</td>
<td>0.79 (0.5-1.2)</td>
<td>0.79 (0.5-1.1)</td>
<td>1.92 (0.7-4.4)</td>
</tr>
<tr>
<td>Median time to best response (95% CI)</td>
<td>2.22 (1.9-3.0)</td>
<td>2.58 (1.9-3.9)</td>
<td>1.41 (0.8-2.4)</td>
</tr>
<tr>
<td>MRD negativity, n (%)</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>R0, n (%)</td>
<td>7 (70.0)</td>
<td>5 (71.4)</td>
<td>2 (66.7)</td>
</tr>
</tbody>
</table>

---

**LEUKEMIA & LYMPHOMA SOCIETY™**
TIMING OF B-CELL MUTATION ANTIGEN (BCMA)-TARGETING TREATMENT

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Total cilta-cel N=18*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders N = 12</td>
<td>Non-responders N = 6</td>
</tr>
<tr>
<td>Duration of last anti-BCMA treatment, days</td>
<td>29.5</td>
<td>63.5</td>
</tr>
<tr>
<td>Median</td>
<td>1-277</td>
<td>22-527</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from last anti-BCMA treatment to apheresis, days</td>
<td>161.0</td>
<td>56.5</td>
</tr>
<tr>
<td>Median</td>
<td>26-695</td>
<td>40-895</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from last anti-BCMA treatment and cilta-cel infusion, days</td>
<td>235.0</td>
<td>117.5</td>
</tr>
<tr>
<td>Median</td>
<td>62-749</td>
<td>95-944</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Two patients died before confirmed disease evaluations and were excluded from the analysis.

Cohen, A et al Blood 2023

IMMUNOBIOLOGY AND IMMUNOTHERAPY | MARCH 21, 2023

Sequencing T-cell redirection therapies leads to deep and durable responses in patients with relapsed/refractory myeloma

Tarek H. Mouhieddine, Oliver Van Oekelen, David T. Melnekoff, Jeanne Li, Yogita Ghodke-Purainik, Guido Lancman, Santiago Thibaud, Darren Pan, Sridavi Rajeeva, Sarita Agte, Adolfo Aleman, Larysa Sanchez, Shambavi Richard, Adriana Rossi, Joshua Richter, Heam Jay Cho, Cesar Rodriguez, Alessandro Lagana, Erin Mosher, Ajai Chari, Sundar Jagannath, Samir Parekh

- 58 Patients progressing after Bispecific Ab therapy.
  - Median of 6 prior therapy lines
  - 89% were triple-class refractory
  - 44% were penta-drug refractory
- Patients were followed for a median of 30.5 months and received a median of 2 additional salvage therapies (range, 1-9).
T-cell redirection therapy as first or second salvage was feasible and associated with a median PFS1 of 28.9 months, PFS2 of 30.9 months, and an OS of 62% at 2 years.
Salvage therapy with T-cell redirection enhances OS

(A) OS of the full cohort of 58 patients (mOS 21.3 mos)

(B) OS of 19 patients receiving T-cell redirection as the FST (mOS NR)

(C) OS of 28 patients receiving T-cell redirection as FST or SST (mOS NR) vs all others (mOS 9.6 mos)
## RESULTS: PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Patients Characteristics</th>
<th>N = 106</th>
<th>MTeC-1 (n=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>66.5 (35-87)</td>
<td>64 (33-84)</td>
</tr>
<tr>
<td>Age &gt;70 years, n (%)</td>
<td>34 (32)</td>
<td></td>
</tr>
<tr>
<td>Median time since diagnosis, years (range)</td>
<td>5.5 (0.5-20)</td>
<td>6.0 (0.8-22.7)</td>
</tr>
<tr>
<td>Number of prior lines of therapy (median, range)</td>
<td>6 (4–17)</td>
<td>5 (2-14)</td>
</tr>
<tr>
<td>&gt;4 prior LOT, n (%)</td>
<td>80 (75)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White, n (%)</td>
<td>72 (68)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Non-Hispanic Black, n (%)</td>
<td>28 (26)</td>
<td></td>
</tr>
<tr>
<td>R-ISS stage III, n (%)</td>
<td>2580 (21)</td>
<td>20162 (12)</td>
</tr>
<tr>
<td>ECOG Performance Status ≥2, n (%)</td>
<td>35 (33)</td>
<td>--</td>
</tr>
<tr>
<td>High-risk cytogenetics, n (%)</td>
<td>5695 (59)</td>
<td>38148 (28)</td>
</tr>
<tr>
<td>Extramedullary disease (EMD), n (%)</td>
<td>45 (42)</td>
<td>28 (17)</td>
</tr>
<tr>
<td>Refractory status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Triple Refractory, n (%)</td>
<td>97 (92)</td>
<td>88 (64)</td>
</tr>
<tr>
<td>• Penta refractory, n (%)</td>
<td>68 (64)</td>
<td></td>
</tr>
<tr>
<td>Prior BCMA-directed Therapy</td>
<td>56 (53)</td>
<td>--</td>
</tr>
<tr>
<td>Prior autologous stem cell transplant, n (%)</td>
<td>61 (58)</td>
<td>135 (82)</td>
</tr>
<tr>
<td>Prior allogeneic stem cell transplant, n (%)</td>
<td>3 (3)</td>
<td></td>
</tr>
</tbody>
</table>

---

## RESULTS: RESPONSE TO TECLISTAMAB

<table>
<thead>
<tr>
<th>Response (Full Cohort)</th>
<th>RWE cohort N=104</th>
<th>MajesTec-1 N=165</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>70 (66)</td>
<td>104 (63)</td>
</tr>
<tr>
<td>Complete response or better</td>
<td>31 (29)</td>
<td>65 (39.4)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>18 (17)</td>
<td>32 (19.4)</td>
</tr>
<tr>
<td>Partial response</td>
<td>21 (20)</td>
<td>7 (4.2)</td>
</tr>
<tr>
<td>Minimal response</td>
<td>0</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (9.5)</td>
<td>27 (16.4)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>26 (24.5)</td>
<td>24 (14.5)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>8 (4.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroups of Interest</th>
<th>ORR, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&gt;70 (n=34)</td>
<td>24 (71)</td>
</tr>
<tr>
<td>Non-Hispanic Black (n=28)</td>
<td>20 (71)</td>
</tr>
<tr>
<td>Pts ineligible for MajesTec-1 trial (n=85)</td>
<td>53 (60)</td>
</tr>
<tr>
<td>High-risk cytogenetics (n=56)</td>
<td>35 (63)</td>
</tr>
<tr>
<td>Triple Refractory (n=97)</td>
<td>62 (64)</td>
</tr>
<tr>
<td>Penta refractory (n=68)</td>
<td>46 (68)</td>
</tr>
<tr>
<td>Prior BCMA therapy</td>
<td>33 (59)</td>
</tr>
<tr>
<td>R-ISS III (n=25)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>EMD (n=45)</td>
<td>21 (47)</td>
</tr>
<tr>
<td>Four or less prior LOT (n=26)</td>
<td>21 (81)</td>
</tr>
<tr>
<td>&gt;4 lines of prior therapy (n=80)</td>
<td>49 (61)</td>
</tr>
</tbody>
</table>
RESULTS: RESPONSE RATES TO TECLISTAMAB BY SPECIFIC TYPE OF PRIOR BCMA-DIRECTED THERAPY

Responders had a longer time since their last BCMA-DT (339 vs 205 days; \(p=0.072\)), c/t non-responders

Pts who started TEC within 3 mo from their last BCMA-DT had a lower ORR (42.9% vs 64.3%; \(p=0.27\))

TALQUETAMAB

"Among the 16 patients who received the doses recommended for a phase 2 study and who had had previous exposure to T-cell Redirecting B-cell maturation antigen (BCMA)–directed bispecific antibodies or chimeric antigen receptor (CAR) T-cell therapies, 8 (50%) had a response."
SUMMARY IN BCMA EXPOSED

<table>
<thead>
<tr>
<th>Product</th>
<th>ORR in general population</th>
<th>Cohort size</th>
<th>ORR with previous BCMA targeted therapy</th>
<th>Difference in ORR</th>
<th>NCT #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teclistamab</td>
<td>63%</td>
<td>25</td>
<td>40%</td>
<td>23%</td>
<td>NCT04557098</td>
</tr>
<tr>
<td>Elranatamab</td>
<td>61%</td>
<td>13</td>
<td>54%</td>
<td>7%</td>
<td>NCT04649359</td>
</tr>
<tr>
<td>Talquetamab</td>
<td>70%</td>
<td>16</td>
<td>50%</td>
<td>20%</td>
<td>NCT03399799</td>
</tr>
<tr>
<td>Talquetamab + Daratumumab</td>
<td>78%</td>
<td>25</td>
<td>72%</td>
<td>6%</td>
<td>NCT04108195</td>
</tr>
<tr>
<td>Cevostamab</td>
<td>58%</td>
<td>43</td>
<td>56%</td>
<td>2%</td>
<td>NCT03275103</td>
</tr>
<tr>
<td>Cilta-cel</td>
<td>95%</td>
<td>20</td>
<td>60%</td>
<td>35%</td>
<td>NCT04133636</td>
</tr>
<tr>
<td>Ide-cel</td>
<td>88%</td>
<td>50</td>
<td>74%</td>
<td>14%</td>
<td>*real world comparison</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• After treatment with a BiAb or CAR T, one can still exhibit favorable outcomes with T-cell redirection tx.

• Conventional salvage therapy demonstrated significantly lower PFS and OS rates.

• There was no statistically significant difference in PFS1 and OS between patients receiving a BiAb or CAR T-cell therapy as FST, indicating that both CAR T cells and BiAbs can have excellent outcomes.
WHEN CHOOSING...

- Duration of therapy
- Dose (i.e. phase 1 clinical trial?)
- Treatment-free interval
- Protein and genomic loss of target at the time of progression
  - Bispecifics are repeatedly targeting the same antigen, as opposed to the more one-and-done CAR Ts

CASE CONTINUED...

- Pt was bridged to CAR T therapy with KD PACE therapy with good response in her plasmacytomas
- 4/26/23: Infusion of ciltacabtagene autoleucel therapy and attained an MRD neg sCR at 10-5 and 10-6
- 11/6/23: Relapsed with spinal cord compression s/p surgical decompression and XRT
- 12/2023: Started on talquetamab
FUTURE DIRECTIONS

- Increasing antigen expression (gamma secretase inhibitor)
- Combine with other therapies (SOC, PD1, etc)
- Improving CART manufacturing, expansion, longevity
- Multiple antigen targeting
- Optimizing place in therapy

Highlights of Myeloma Rounds
Smoldering Myeloma

Edward A. Stadtmauer, MD
Section Chief, Hematologic Malignancies
Roseman, Tarte, Harrow, and Shaffer Families’ President’s Distinguished Professor
University of Pennsylvania Abramson Cancer Center
Philadelphia, PA
DISEASE TRAJECTORY

Nonmalignant Accumulation

- Stroma angiogenesis
- and IL-6 dependent

Malignant Transformation

- Plasma Cell Leukemia
- Extramedullary Disease

Aggressive and Stromal Independent

MGUS

- <10% bone marrow plasma cells
- <30 g/L M-protein
- No SLiM CRAB
- 1%/yr risk of progression to MM

Smoldering Myeloma

- 10-60% bone marrow plasma cells
- No SLiM CRAB
- ≥30 g/L M-protein (IgG or IgA) OR
- ≥500 mg/24 hr urinary protein
- No amyloidosis
- High-Risk: 20, 20, 2
  - 20% PC
  - 2:1 ratio
  - 2 g/dl M-spike

Multiple Myeloma

- Clonal bone marrow ≥10% or bony/extramedullary plasmacytoma
- AND
- Any ≥ 1 SLiM CRAB feature (s):
  - SLiM*: S: Clonal plasma cells in BM ≥60%
    - L: Serum free light-chain ratio ≥100 mg/L
    - M: >1 MRI focal lesion ≥5 mm
  - CRAB* feature:
    - C: Calcium elevation (>11 mg/dL)
    - R: Renal insufficiency (Cr>2 mg/dL or CrCl<40 mL/min)
    - A: Anemia (Hgb<10 g/L)
    - B: Bone disease: (≥1 lytic lesion)

SMOLDERING MYELOMA CLINICAL CASE

- 67-year-old male with history of synchronous NSCLC, CKD, HTN, T2DM
- Followed with local oncologist for NSCLC – was treated with RUL and RML lobectomies, followed by 4 cycles of adjuvant chemotherapy (cisplatin/pemetrexed), completed in 2020.
- Followed by nephrologist for CKD
- 2021 – UPEP shows monoclonal protein (118.88 mg/dL), SPEP negative
- 2022 – kidney function stable, full plasma cell dyscrasia workup is performed
- Initial Lab Evaluation
  - WBC: 12.1; Hgb: 16; Plt: 270, Creatinine: 1.76 mg/dL, Calcium: 10.5 mg/dL, SPEP: 0.1 g/dL monoclonal free lambda. UPEP (24 hr): 146.45 mg/dL monoclonal free lambda. Serum free lambda: 1911; serum free kappa: 35.5; ratio: 0.02, IgM: 35; IgA: 142; IgG: 1028, LDH: 180 units/L, Albumin: 4.8 g/dL, Beta 2 microglobulin: 3.30 mcg/mL
  - CT chest/abdomen/pelvis (performed for lung cancer surveillance): No osseous abnormalities. Complete skeletal survey: No lytic or blastic lesions
  - Bone Marrow Biopsy and FISH: Plasma cell disorder – monoclonal lambda plasma cells comprising 15% of marrow, Congo red negative, FISH – negative for multiple myeloma panel

SHOULD WE TREAT HIGH-RISK SMOLDERING MYELOMA?

- Len-dex vs observation in high-risk SMM.
- Overall survival benefit to early treatment, but...
  - Control arm did not receive lenalidomide-based therapy at progression.
  - Treatment was withheld from control arm until CRAB features developed.
  - Advanced imaging was not used to assess for lytic bone lesions
Multiple myeloma is highly complex during progression and relapse due to genomic events and clonal evolution.

**THE TRAJECTORY OF MYELOMA**

- **Asymptomatic**
  - MGUS or smoldering myeloma
  - M protein (g/L)
- **Symptomatic**
  - ACTIVE MYELOMA
  - 1. RELAPSE
  - Plateau remission
  - 2. RELAPSE
  - REFRACTORY RELAPSE

**First-line therapy**
**Second line**
**Third line**

- **1. RELAPSE**
- **2. RELAPSE**
- **REFRACTORY RELAPSE**

**SHOULD WE TREAT HIGH-RISK SMOLDERING MYELOMA?**

ECOG E3A06: Int-high risk SMM* → Randomize lenalidomide vs observation

PFS by Mayo risk subgroups (2/20/20)

- **High**
  - Len (N=25)
  - Obs (N=31)
  - In HR subset, most progression occurred in first 9M
  - No difference in overall survival at 36M followup

- **Low**

**Comparison Table**

<table>
<thead>
<tr>
<th></th>
<th>Len (n=90)</th>
<th>Obs (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since SMM dx (med)</td>
<td>2.6 mos.</td>
<td>3.4 mos.</td>
</tr>
<tr>
<td>High-risk subset</td>
<td>1.3 mos.</td>
<td>0.9 mos.</td>
</tr>
<tr>
<td>Progression events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Bone lesions or plasmacytoma</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

*BMPC >10% + abnormal SFLC ratio

1 fatal PE in lenalidomide arm

Lonial et al JCO 2019
FINAL ANALYSIS OF CENTAURUS: STUDY DESIGN

- Randomized, open-label phase II study
  - Also stratified by: <2 vs ≥ 2 risk factors
  - Long Intense
    - Cycle 1: QW (n = 41)
    - Cycle 2-3: Q2W
    - Cycle 2-4: Q4W
    - Cycle 8-20: Q8W
  - Intermediate
    - Cycle 1: QW (n = 41)
  - Short Intense
    - Cycle 1: QW (n = 41)
  - In all arms: daratumumab 16 mg/kg IV in 8-wk cycles; option to switch to SC during extension after study amendment

- Primary endpoint: ≥ CR, PD, or death per PY
- Secondary endpoints: ORR, PFS, OS

*Risk criteria: BM plasma cells ≥10% AND ≥1 g/dl; serum M-protein ≥3 g/dl (l ≥2 g/dl), urine M-protein >500 mg/24 hr, abnormal FLC ratio (<0.126 or >8) with serum M-protein >1 to <3 g/dl, absolute involved sFLC ≥100 mg/l with abnormal FLC ratio (<0.126 or >8)

FINAL ANALYSIS OF CENTAURUS

<table>
<thead>
<tr>
<th>Investigator-Assessed Response</th>
<th>Long (n = 41)</th>
<th>Intermediate (n = 41)</th>
<th>Short (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>58.5</td>
<td>53.7</td>
<td>37.5</td>
</tr>
<tr>
<td>sCR</td>
<td>4.9</td>
<td>7.3</td>
<td>0</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td>VGPR</td>
<td>24.4</td>
<td>14.6</td>
<td>20.0</td>
</tr>
<tr>
<td>PR</td>
<td>29.3</td>
<td>29.3</td>
<td>17.5</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>NR*</td>
<td>83.4*</td>
<td>72.7*</td>
</tr>
</tbody>
</table>

- PFS, mo
  - Median PFS (per protocol) NR NR NR
  - Including extension phase NR 84.4 74.1

- OS
  - Median, mo NR NR NR
  - 84-mo, % 81.3 89.5 88.1
  - Events, n (%) 7 (17.1) 5 (12.2) 4 (9.8)
  - Median time to next treatment, mo NR NR 76.3

- At median follow-up of ~7 yr, daratumumab monotherapy continued to show clinical activity in patients with intermediate- or high-risk SMM
  - Trend toward longer PFS and time to next treatment with long-intense dosing schedule
  - No new safety concerns observed with extended daratumumab exposure
SHOULD WE TREAT HIGH-RISK SMOLDERING MYELOMA?

- Many trials are investigating early treatment strategies
- In our opinion, current evidence does not favor early treatment
  - PFS as reported is not a clinically relevant endpoint
  - PFS benefit in E3A06 may be driven by SMM patients actively evolving to
  - OS benefit in QuiReDex may be due to absence of lenalidomide in observation arm at progression
- FDA has not approved any therapy for treatment of smoldering multiple myeloma
- Excellent discussion of these data: Raje and Yee, JCO 38:11 (2020) 119-1125.

PATIENT SUMMARY

- 10% BMPC
- M-spike: <3 g/dL
- SFLCR: 0.02
- Mild hypercalcemia
- CKD of unclear etiology
- No anemia
- No bone lesions
- Kidney Biopsy: Global glomerulosclerosis, moderate, with glomerulopathy, Tubular atrophy and interstitial fibrosis, moderate, Arterio- and arteriolo-sclerosis and hyalinosis, moderate, Immunofluorescence microscopy is negative for paraprotein or significant immune complex deposition
- Management
  - Deferred initiation of treatment. Risk stratification: intermediate risk based on SFLCR (1 of 3 of the 20-2-20 criteria). No indication for smoldering myeloma treatment given not high-risk disease, Clinical evaluation and lab monitoring every 3 months
Thank You!

FREE LLS RESOURCES FOR HEALTHCARE PROVIDERS

- CME & CE courses: www.LLS.org/CE
- Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- Videos for HCPs: www.LLS.org/HCPvideos
- Podcast series for HCPs: www.LLS.org/HCPpodcast
FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).
  - www.LLS.org/IRC
- **Clinical Trial Nurse Navigators** – RNs and NPs provide a personalized service for patients seeking treatment in a clinical trial, sift through the information and provide information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC
- **Nutrition Education Services Center** – one-on-one consultation with a registered dietician for patients/caregivers of all cancer types (NESC).
  - www.LLS.org/Nutrition
- **Reach out** Monday–Friday, 9 am to 9 pm ET
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: www.LLS.org/ContactUs
  - HCP Patient Referral Form: www.LLS.org/HCPreferral

FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **Webcasts, Videos, Podcasts, booklets:**
  - www.LLS.org/Webcasts
  - www.LLS.org/EducationVideos
  - www.LLS.org/Podcast
  - www.LLS.org/Booklets
  - www.LLS.org/Myeloma

- **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
    - Urgent Need
    - Patient Aid
    - Travel Assistance
  - Other Support: www.LLS.org/Support
    - LLS Regions
    - Online Weekly Chats Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program
FREE LLS RESOURCES FOR YOUR PATIENTS

- www.LLS.org/Myelomalink

BOOKLETS AND FACT SHEETS
- English – www.LLS.org/Booklets
- Spanish – www.LLS.org/Materiales

We have one goal: A world without blood cancers

THANK YOU

ANY QUESTIONS?
SEND TO PROFEDUCATION@LLS.ORG